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Prevention of meningococcal disease during the Hajj and Umrah mass gatherings: past and current measures and future prospects

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SUMMARY

The Kingdom of Saudi Arabia (KSA) has a long history of instituting preventative measures against meningococcal disease (MD). KSA is at risk of outbreaks of MD due to its geographic location, demography, and especially because it hosts the annual Hajj and Umrah mass gatherings. Preventative measures for Hajj and Umrah include vaccination, targeted chemoprophylaxis, health awareness and educational campaigns, as well as an active disease surveillance and response system. Preventative measures have been introduced and updated in accordance with changes in the epidemiology of MD and available preventative tools. The mandatory meningococcal vaccination policy for pilgrims has possibly been the major factor in preventing outbreaks during the pilgrimages. The policy of chemoprophylaxis for all pilgrims arriving from the African meningitis belt has also probably been important in reducing the carriage and transmission of *Neisseria meningitidis* in KSA and beyond. The preventative measures for Hajj and Umrah are likely to continue to focus on vaccination, but to favour the conjugate vaccine for its extra benefits over the polysaccharide vaccines. Additionally, the surveillance system will continue to be strengthened to ensure early detection and response to cases and outbreaks; ongoing disease awareness campaigns for pilgrims will continue, as will chemoprophylaxis for target groups. Local and worldwide surveillance of the disease and drug-resistant *N. meningitidis* are crucial in informing future recommendations for vaccination, chemoprophylaxis, and treatment. Preventative measures should be reviewed regularly and updated accordingly, and compliance with these measures should be monitored and enhanced to prevent MD during Hajj and Umrah, as well as local and international outbreaks.

1. Introduction

Meningococcal disease (MD) refers to the spectrum of dangerous infections caused by *Neisseria meningitidis*, including meningitis, bacteraemia, and pneumonia. The rapidity of the disease and difficulty distinguishing it from other febrile infections may result in delayed diagnosis with high morbidity and mortality.[1] Thirteen serogroups of *N. meningitidis* have been reported, but only six serogroups (A, B, C, W135, X, and Y) are responsible for the great majority of invasive disease worldwide.[2] Due to the seriousness of MD, its disabling sequelae, and the potential for epidemic spread, a single case of MD elicits an urgent public health response. This is particularly important during global events with a risk for international spread. The Hajj and Umrah religious mass gatherings in the Kingdom of Saudi Arabia (KSA) are a case in point. These events annually draw millions of Muslims from over 180 different countries to the holy cities of Mecca and Medina for the pilgrimages. The prevention of MD during Hajj and Umrah is of the utmost importance for global health security, yet it is extremely challenging given the large numbers of pilgrims participating, the different disease epidemiology profiles in their countries of origin, and the crowded conditions during these events. Hajj and Umrah promote the acquisition of meningococcal carriage and also disease transmission, and have historically been linked to a number of local and international meningococcal outbreaks.[3,4]

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Measures to prevent MD during Hajj and Umrah have been introduced over the years and have been updated and modified in accordance with changes in the epidemiology of the disease and available data and preventative tools (Figure 1). Supporting these preventative measures is a well-established and long-standing disease surveillance system in KSA to characterize MD epidemiology (dating back to 1970). It includes a standard clinical case definition, field investigation of cases and outbreaks, tracing of contacts, and laboratory capacity for the confirmation and characterization of *N. meningitidis*, as recommended by the World Health Organization (WHO).[5] In KSA, the Public Health Department, within the Ministry of Health, runs the surveillance system for rapid reporting of suspected meningitis cases in each of the 20 Health Affairs directorates, with detailed case-reporting required for all confirmed cases. Laboratory confirmation depends on either isolation of the causative organism, from cerebrospinal fluid (CSF) or by blood culture, or by detection of antigen in a normally sterile site such as the CSF.[6] This surveillance system is enhanced during each Hajj, especially where pilgrims reside or visit, to include in addition to the standard case reporting, active case finding and tracing of contacts for prompt management and control and real-time updates on suspected or confirmed cases.

The carriage of *N. meningitidis* among pilgrims and their contacts and MD and outbreaks during the Hajj and Umrah mass gatherings have been reviewed previously.[3,4] In this review, the preventative measures implemented by the Saudi health authorities to prevent MD during these events are examined, highlighting the past and current strategies and forecasting possible future changes.

2. Prevention of meningococcal disease

In the absence of a vaccine that protects against all serogroups of *N. meningitidis*, MD preventative measures are multifactorial and rely on effective disease surveillance and response, the rapid generation of reliable epidemiological data, and the implementation of appropriate vaccination policies, chemoprophylaxis for at-risk groups, and focussed educational and awareness campaigns. Vaccination is the most effective way of preventing MD. The WHO recommends that countries with either intermediate–high endemic disease rates (≥2 cases/100 000 population/year) or frequent epidemics (irrespective of endemicity) should introduce appropriate large-scale meningococcal vaccination programmes. In countries where the disease occurs less frequently (<2 cases/100 000 population/year), meningococcal vaccination is recommended for groups at high risk of meningococcal exposure and disease, including travellers to high-endemic areas.[5]

The ideal meningococcal vaccine would be affordable and effective against all serogroups of meningococci, would elicit long-lasting immunity in all age groups, especially infants, children, and adolescents, and importantly, would provide significant herd immunity.[2] Unfortunately, although attempts at vaccine development go as far back as the early 1900s,[7] and licensed vaccines have been available since the 1970s, no such vaccine yet exists.[5,7] Currently available meningococcal vaccines include polysaccharide and polysaccharide–protein conjugate vaccines; both are available against meningococci of serogroups A, C, W135, and Y.[8]

Internationally marketed meningococcal polysaccharide vaccines are based on purified, heat-stable, lyophilized capsular polysaccharides derived from meningococci of the respective serogroup and include bivalent (A,C), trivalent (A, C, W135), and quadrivalent (A, C, W135,Y) formulations.[7,8] Licensed meningococcal conjugate vaccines are based on conjugation of polysaccharides to protein carriers.[7] They include monovalent (A or C) and quadrivalent (A, C, W135,Y) vaccines, and also a combination vaccine based on *Haemophilus influenzae* type b and *N. meningitidis* serogroup C (HibMenC).[8,9] The first quadrivalent (A/C/W/Y) meningococcal conjugate vaccine was licensed in 2005 and more have been licensed since.[5,7,8]

The development of vaccines for broad protection against serogroup B disease has presented challenges because the native B polysaccharide potentially cross-reacts with human antigens and is poorly immunogenic; in addition, other potential antigen targets of group B meningococci are highly diverse.[5,10] B vaccines have been developed using outer membrane vesicles (OMVs) prepared from specific (clonal) outbreak B strains,[7] and have been successfully deployed to control epidemics in Norway, Cuba, New Zealand, and France.[7,10] The OMV vaccines are immunogenic, but require multiple doses, especially in infants, and appear to induce protection of relatively short duration.[7] Efforts to find novel vaccine antigens to protect against serogroup B disease have led to a number of vaccine candidates that are currently under investigation in clinical trials.[7,10] Two of these vaccines are licensed in a few countries and recommended for certain risk groups and have been used to control outbreaks.[11,12] No vaccine is available against disease caused by serogroup X meningococci.[5]

Polysaccharide vaccines are essentially T-cell independent antigens, hence they are weakly immunogenic (especially in infants), induce a poor immunological memory response, and provide a relatively short duration of protection.[7,9] Polysaccharide vaccines do not reliably reduce the carriage rate, nor do they prevent the spread of meningococci by asymptomatic carriers.[5,13] In addition, they cannot be boosted; in fact, repeated polysaccharide vaccinations can result in a reduced immune response (hyporesponsiveness).[5,9,13] The conjugate vaccines are more immunogenic and induce immunological memory.[9] Repeated doses with quadrivalent meningococcal conjugate vaccines do not result in hypo-responsiveness but show a clear booster effect. They have the potential to reduce the carrier rate and hence may contribute to the reduction of *N. meningitidis* transmission.[7,8]

Various meningococcal vaccines are used in different countries depending on the national epidemiology, socioeconomic resources, licensing laws, and national recommendations.[5,8] Due to the high cost of conjugate vaccines, the WHO endorses the use of polysaccharide vaccines in mass vaccinations to control outbreaks in countries with limited economic resources or an insufficient supply of meningococcal conjugate vaccines. However, due to the limited efficacy of polysaccharide vaccines in children <2 years of age, in confirmed group A or C outbreaks the appropriate monovalent conjugate serogroup A and C vaccines should be used for protection of those aged 12–24 months and 2–24 months, respectively.[5]

Chemoprophylaxis for at-risk individuals is also a key component of MD prevention. Close contacts of cases are at risk of secondary disease. Antibiotics are effective in preventing additional cases through eradicating carriage of the invasive strain so that transmission is prevented. Antibiotic chemoprophylaxis is used to prevent disease in close contacts of cases and can be offered to at-risk individuals during outbreaks.[5] Mass chemoprophylaxis is also used in target populations on arrival to Saudi Arabia for the Hajj and Umrah pilgrimages.[14] Ciprofloxacin, ceftriaxone, rifampicin, and azithromycin are all effective for chemoprophylaxis,[5,15,16] but ciprofloxacin is the agent of choice because it can be used as a single dose and lacks toxicity.[17]

3. Hajj and Umrah meningococcal disease preventative measures: past and current policies and compliance

3.1. Past strategies

Meningococcal vaccines have been available in KSA since the 1970s, and until 1987, vaccination against MD was only required